Remote C6 Selective Ruthenium-Catalyzed C-H Alkylation of Indole Derivatives *via* σ-Activation

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ABSTRACT: The site-selective functionalization of an indole template offers exciting possibilities for the derivatization of molecules with useful biological properties. Herein, we report the remote C6 selective C-H alkylation of indole derivatives enabled by ruthenium(II) catalysis. Remote alkylation was achieved using *N*-pyrimidinyl indoles with an ancillary ester directing group at the C3 position. This ancillary directing group proved pivotal to reactivity at C6, with yields up to 92% achieved. A one-pot procedure to install this directing group followed by remote C6 functionalization has also been reported, both shown to proceed *via* ruthenium redox catalysis. Computationally calculated Fukui indices elucidated that the C6 position to be the most reactive vacant C-H site towards potential functionalization. When coupled with deuterium incorporation studies, a C2 cyclometalation/remote σ-activation pathway was deduced.

KEYWORDS: Ruthenium, Homogeneous Catalysis, Indole, Heteroaromatics, Remote Functionalization

Introduction

The development of transition metal catalyzed C-H functionalization has emerged as a very powerful tool to synthesize and derivate biologically interesting molecules.[1] The indole heteroaromatic has received great attention over the past century due to their prevalence in a large number of natural products, pharmaceuticals and agrochemicals.[2] Because of this, the development of elegant methods for the synthesis of highly decorated indoles has received huge efforts in recent years.[3] Due to the high potential of these motifs, indoles have been widely used as C-H activation templates. The C3 position has been shown to be the C-H bond with the most intrinsic reactivity in direct transition metal catalyzed C-H functionalization (Figure 1).[4] C2 functionalization has been achieved using a variety of metal systems, primarily through functionalization of the NH bond with a directing group. Here cyclometalation is facilitated *via* chelation assistance to afford C-H insertion and subsequent functionalization at C2.[5]

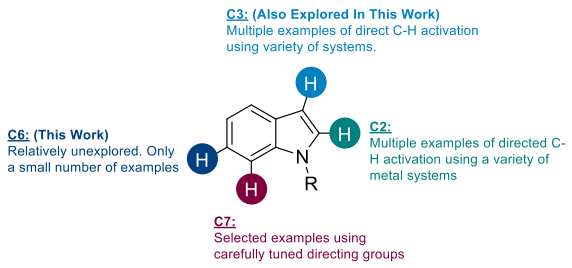


Figure 1: Current sites of C-H functionalization of indoles.

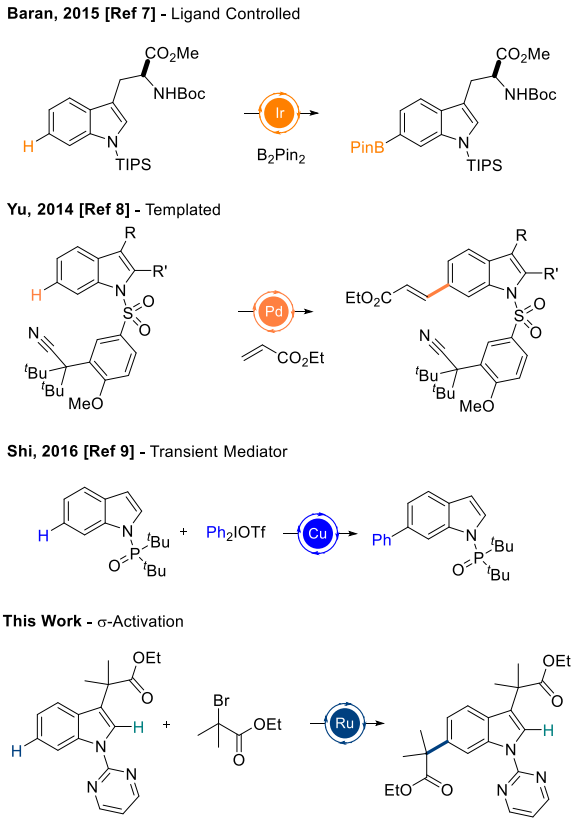
Additionally, carefully designed phosphonate directing groups have also granted access to C7 functionalized indoles in selected examples.[6]

Remote reactivity at C6 of an indole has only been sparingly observed. Selected examples include the use of ligand controlled iridium catalysis by Baran,[7] templated C-H insertion by Yu,[8] and elegant studies by Shi and co-workers combining the phosphonate directing group and other remote functionalization techniques (Scheme 1).[9] The ability to access remote unreactive C-H bonds has been a great challenge to catalytic chemists in recent years.[10] Despite this, a few methods have prevailed: meticulous template design,[11] metal-directed σ-activation,[12] the use of a transient mediator,[13] and the careful manipulation of steric/electronic effects (albeit sparingly). [14] The use of σ-activation lends itself as the most atom-economical versus the other two methods which often lead to high quantities of waste product streams. This is especially the case in the templated work where often templates are pre-synthesized, installed and then removed.[11]

Our previous work in the area depicts the remote *meta*-alkylation of 2-phenylpyridine using the α-bromo ester coupling partner.[12c] This was postulated to proceed *via* an *ortho*-cyclometalation which promotes a remote σ-activation *para*- to metal insertion to afford net *meta*-substituted products. Herein, we report the expansion of this methodology away from privileged structures such as 2-phenylpyridine to biologically relevant structures such as indoles. Ackermann and co-workers have recently explored the use of pyrimidinyl-substituted anilines in *meta*-functionalization[12d] and the expansion of motifs for remote activation is pivotal in moving towards

broadly useful synthetic methodology. Here we have developed the remote C6 selective ruthenium-catalyzed C-H alkylation of pyrimidinyl-indole derivatives. It is proposed to proceed *via* a C2 cyclometalation σ-activation pathway utilizing an ancillary directing group present at the C3 position

Scheme 1. Previous work on remote transition metal catalyzed C-H functionalization of indoles

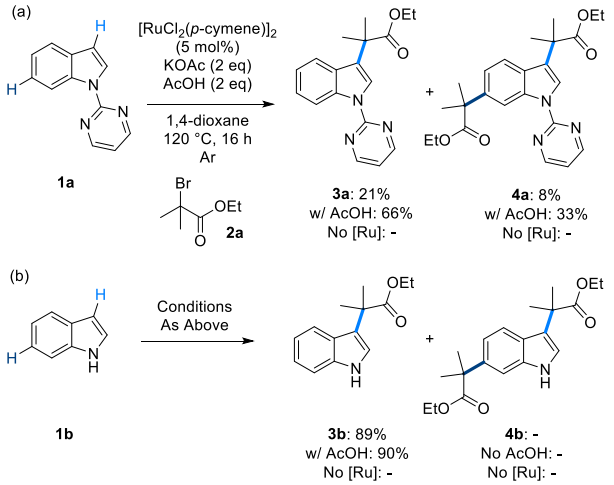


Results & Discussion

The investigation into the remote functionalization of indole derivatives began by applying our previous *meta*-alkylation conditions with 1-(pyrimidin-2-yl)-indole (**1a**, Scheme 2a).[12c] This gave rise to two products, primarily C3 alkylated indole motif (**3a**) and interestingly the C3/C6 di-alkylated structure was also observed (**4a**). Pleasingly, quantitative conversion of starting material **1a** to **3a** and **4a** was observed on addition of acetic acid to the reaction mixture. The regioselectivity of functionalization was further confirmed *via* single crystal X-ray crystallography (Figure 2).[15]

In the absence of the ruthenium catalyst no reactivity to either **3a** nor **4a** was maintained, despite the innate reactivity of the C3 position. The use of 1*H*-indole (**1b**, Scheme 2b) in the reaction gave solely the C3 functionalized motif (**3b**) in excellent yields, however showed no selectivity to the C6 position (**4b**). This was also shown not to require the addition of AcOH, however still proceeded by a ruthenium-catalyzed mechanistic pathway. Interestingly, neither *tert*-butoxycarbonyl nor benzyl *N*-substituted indoles gave conversion to either product. This showed that an aromatic nitrogen or NH were vital to any catalytic functionalization, and a strongly coordinating directing group was key to granting access to C6 functionalized motifs. It should be noted that this initial C3 selectivity is complementary to the C2 selectivity that Stephenson and co-workers observed using ruthenium photocatalysis with similar coupling partners.[16]

Scheme 2. Ruthenium(II)-catalyzed C-H alkylation of indoles[a]



[a] Isolated yields after silica gel column chromatography

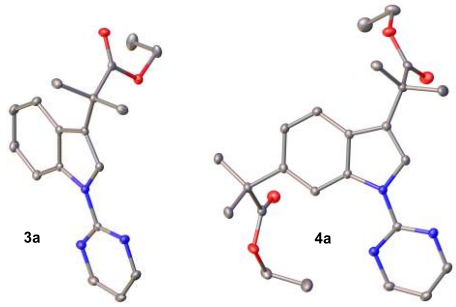
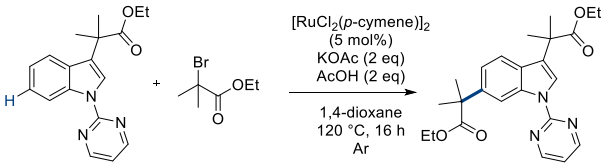


Figure 2: X-ray crystallographic structures of **3a** and **4a** which confirm the functionalization regioselectivity. Ellipsoids as depicted at 30% probability and hydrogen atoms have been omitted for clarity. Atom colors: N, blue; O, red; C, grey.

As there was no observation of indole structures solely functionalized in the C6 position, it was postulated that the C3 structure was an intermediate. This was investigated by resubmitting the C3 product (**3a**) to the reaction conditions. Pleasingly high conversions to di-substituted structure (**4a**) were observed *via* crude NMR analysis (entry 1, Table 1), leading to excellent isolated yields for remote σ-activation reactions.[12] Reaction efficiency was maintained when using THF and 2-MeTHF as solvent (entries 2-3). The reaction was also shown to proceed with modest efficiency without AcOH (entry 5). It is proposed that the added AcOH facilitates protodemetalation at the end of the reaction cycle. However, it's is not vital to reactivity as 2 equivalents are formed in the reaction mixture. Removal of KOAc nullified reactivity (entry 6) however increased loading (4 eq, entry 7) of potassium acetate showed some increased reactivity cf. without AcOH (entry 5). The reaction did not proceed in the absence of ruthenium catalyst (entry 8). This indicates that both C3 and C6 functionalizations are driven by ruthenium catalysis. The synthesis of **3a** was shown to be scalable, affording up to two grams of material (see Scheme S1 in supporting information).

Table 1. Remote ruthenium(II)-catalyzed C6 C-H alkylation of indole derivative



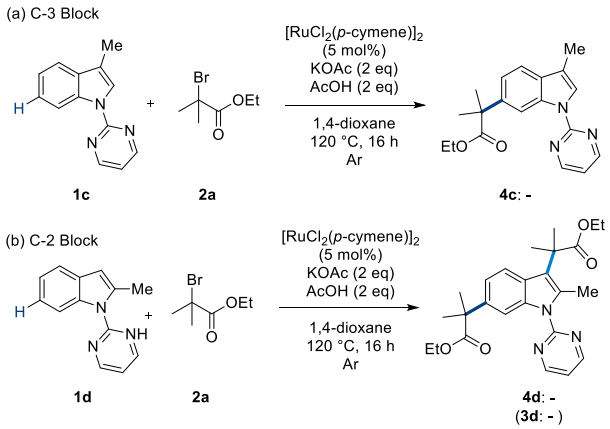
3a 2a 4a

Entry	Alteration from Standard Conditions[a]	4a (%)[b]
1	None	96 (80)[c]
2	THF used as solvent	95
3	2-MeTHF used as solvent	89
4	DME used as solvent	56
5	No AcOH	60
6	No KOAc	-
7	4 eq KOAc, No AcOH	70
8	No $[RuCl_2(p\text{-cymene})]_2$	-
9	Reaction carried out under air	9

[a] Standard Conditions: **3a** (0.25 mmol), **2a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), KOAc (0.5 mmol), AcOH (0.5 mmol), 1,4-dioxane (1 mL), at 120 °C for 16 h under an argon atmosphere. [b] Direct conversion between **3a** and **4a** observed *via* crude NMR analysis. [c] Isolated Yield.

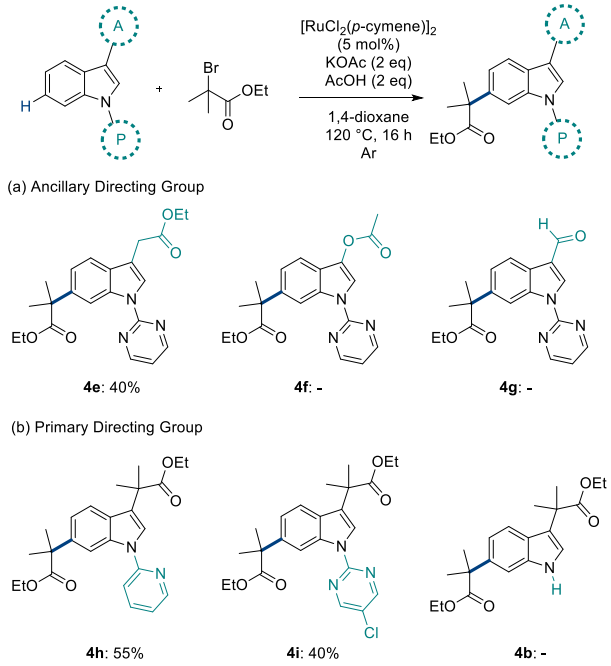
To investigate whether the C3 functionalization solely functioned as a positional block, permitting access to C6 functionalization on steric grounds as the next most reactive site or if the ester group had some ancillary directing group effect, a pyrimidinyl indole bearing a methyl group in the C3 position was submitted to the reaction conditions (**1c**, Scheme 3a). No conversion to any product was observed, which signifies the importance of the nature of the C3 functionality in activating the remote C6 position. A C2-Me blocked substrate was also submitted to the reaction conditions (**1d**, Scheme 3b), giving rise to neither the C3 mono-functionalized nor C3/C6 di-functionalized products. This shows that the C2 cyclometalation site is also necessary for the reaction to proceed.

Scheme 3. Remote C6 functionalization of C3-Me and C2-Me indole derivatives



Using this knowledge further indole derivatives with proposed ancillary directing groups (A) were synthesized (Scheme 4a). Firstly, an auxin derivative, without the gem-dimethyl substituents, was shown to lead to conversion to product (**4e**) albeit in lower quantities. An inseparable, uncharacterisable polymeric byproduct was also obtained with this example, this could be due to the potential radical formed on the benzylic position of the ancillary directing group. Neither acetoxy (**4f**) nor formyl (**4g**) derivatives gave formation of C-6 alkylated product.

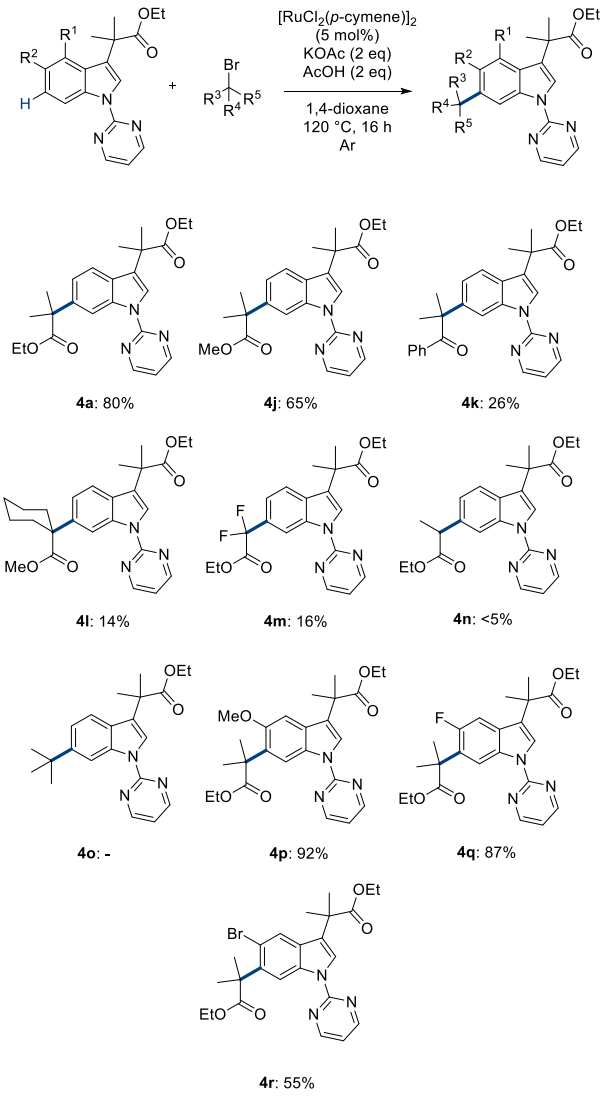
Scheme 4. Ancillary (A) and primary (P) directing group effects of remote C6 functionalization



Further to this, a small screen of primary directing groups (P, Scheme 4b) was investigated. Pyridine (**4h**) and chloro-pyrimidine (**4i**) derivatives gave rise to good yields and the lack of primary directing group (**4b**) gave no conversion to product. This, along with the previous results, highlight the necessity for both the primary and ancillary directing groups for effective catalysis at C6 to take place.

Various tertiary alkyl halides were submitted to the reaction conditions in order to create highly decorated indole structures (Scheme 5). The use of methyl α-bromoisobutyrate granted access to orthogonally functionalized positions with difficult to construct quaternary centers (**4j**). α-bromo ketones have previously been used in ruthenium redox catalysis[17] and were also shown to be amenable to this reaction methodology (**4k**). Fluorinated and cyclohexyl variants of the esters were tolerated (**4l-m**), although in poor yields Unfortunately, secondary esters were shown to give trace formation of C6 alkylated product (**4n**). primary esters, tertiary acids, tertiary amides and tertiary nitriles were not tolerated in this methodology under these reaction conditions (see supporting information).

Scheme 5. Remote C6 functionalization of indole derivatives

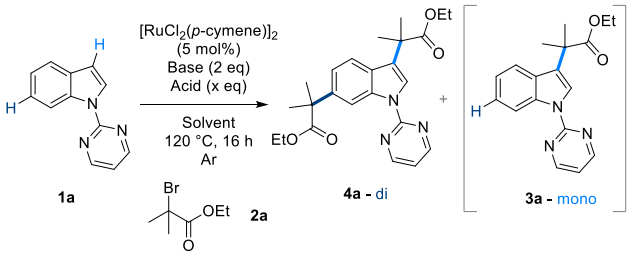


Despite its use previous remote functionalizations,[12c,d] the use of *tert*-butyl bromide as coupling partner also afforded no C6 alkylated motif (**4o**) under these conditions.[18] This shows the unique reactivity of these α-ester radicals through captodative stabilization.[19] Indole structures bearing electron donating groups gave excellent yields (**4p**), whereas electron poor arenes gave poorer yields (**4r**), consistent with our previous reports.[12c] The *ortho*-/*para*- directing character of alkoxy and halogen substituents could have contributed to the improved yields observed by further activation of the C6 position towards radical attack. C4-F substituted indole was shown to react in poor yields, exclusively at C7 (*para*- to the fluorine see supporting information, Scheme S3). This was interpreted to take place *via* radical attack to the organic non-cyclometalated species which was also confirmed *in silico* to be the most reactive vacant site (Figure S1).

It is possible to access the C3/C6 di functionalized motif (**4a**) directly from the unsubstituted indole derivative (**1a**). This allows one-pot ruthenium(II)-catalyzed C3 C-H alkylation and subsequent C3 enabled remote C6 selective C-H alkylation. Conditions were explored to drive the reaction methodology to the di-substituted motif (**4a**, Table 2).

A solvent screen showed that the use of THF led to more favorable formation of di-functionalized product (entry 5). Several different bases (entries 7 -10) and acids (entries 11-12) were used in the reaction however none gave superior conversion to the KOAc/AcOH couple. The reaction system using K_2CO_3 as base (entry 8) was however shown to be reactivated on addition of catalytic quantities of KOAc (entry 9). This clearly demonstrates the need for a carboxylate partner for C-H metalation to take place at start the reaction.[1a] Interestingly it was shown increasing addition of AcOH correlated to increased selectivity towards mono-functionalized product **3a**. This was exemplified by use of AcOH as solvent (entry 15) which led to almost exclusive formation of **3a**. This highlights the importance of AcOH in the C3 functionalization of the pyrimidinyl substituted indole (**1a**), but is then detrimental to C6 functionalization in high quantities. This demonstrates that it is a careful balance of acid and base that drives to di-functionalization (**4a**).

Table 2. Optimization of ruthenium(II)-catalyzed C3 C-H alkylation of indole derivatives



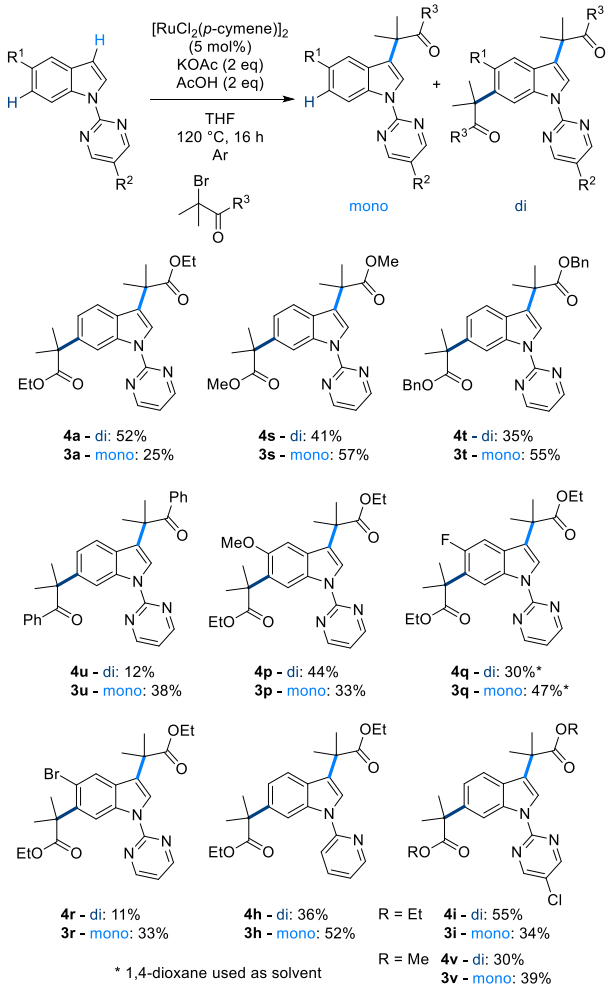
Entry	Solvent	Base	Acid	Acid Eq	4a (%)[b]	3a (%)[b]
1[c]	1,4-dioxane	KOAc	-	-	8	21
2[c]	1,4-dioxane	KOAc	AcOH	2	33	66
3	2-MeTHF	KOAc	AcOH	2	34	62
4	DME	KOAc	AcOH	2	45	48
5	**THF**	**KOAc**	**AcOH**	**2**	**57**	**39**
6	THF	-	AcOH	2	0	26
7	THF	NaOAc	AcOH	2	9	35
8	THF	K_2CO_3	AcOH	2	3	6
9	THF	K_2CO_3[d]	AcOH	2	43	46
10	THF	KOPiv	AcOH	2	9	17
11	THF	KOAc	PivOH	2	32	65
12	THF	KOAc	TFA	2	3	31
13	THF	KOAc	AcOH	3	46	56
14	THF	KOAc	AcOH	10	31	69
15	THF	KOAc	AcOH	33[e]	5	91

[a] General Conditions: 1-(pyrimin-2-yl)-1*H*-indole (**1a**, 0.25 mmol), ethyl α-bromoisobutyrate (0.75 mmol), [RuCl²(*p*-cymene)]₂ (0.0125 mmol, 5 mol%), Base (2 eq), Additive (x eq), Solvent (1 mL), 120 °C, 16 h under argon atmosphere. [b] Direct ¹H NMR conversion. [c] From Scheme 2 for comparison. [d] + KOAc (30 mol%). [e] AcOH used as solvent instead of THF.

The scope of the one-pot C3 and subsequent C6 functionalization was then explored (Scheme 6). 5-substituted indoles (**4n-p**) gave one-pot reactivity parallel to the C6 functionalization shown previously with the electron rich structure performing most efficiently. The pyridine directing group (**4h**) was shown to be amenable to this reaction albeit in slightly lower yields with respect to the pyrimidine counterpart. The

use of the 5-chloropyrimidine directing group (**4i**) led to the highest yield of one-pot C3 and subsequent C6 alkylation. This ability to carry out this double C-H functionalization allows simple quick diversification to create highly decorated complex structures.[20] The mono-functionalized structures have also been shown to be amenable to resubmission to the reaction conditions to drive formation of the di-functionalized motif or reacted with a different coupling partner to give orthogonal C-H functionalization.

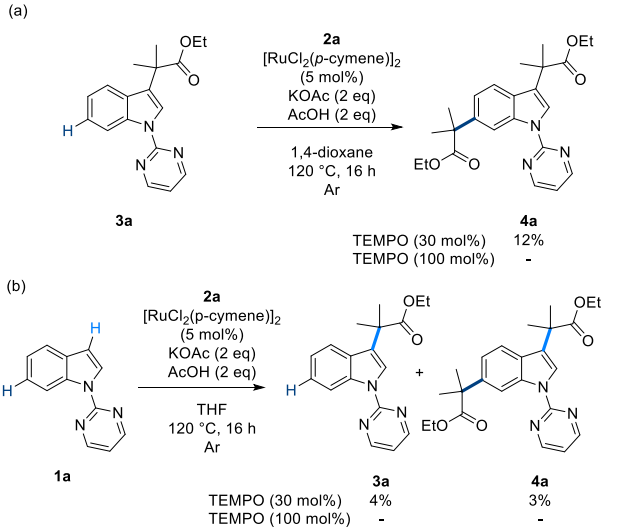
Scheme 6. One-Pot C3/C6 functionalization of indole derivatives



Mechanistic Studies

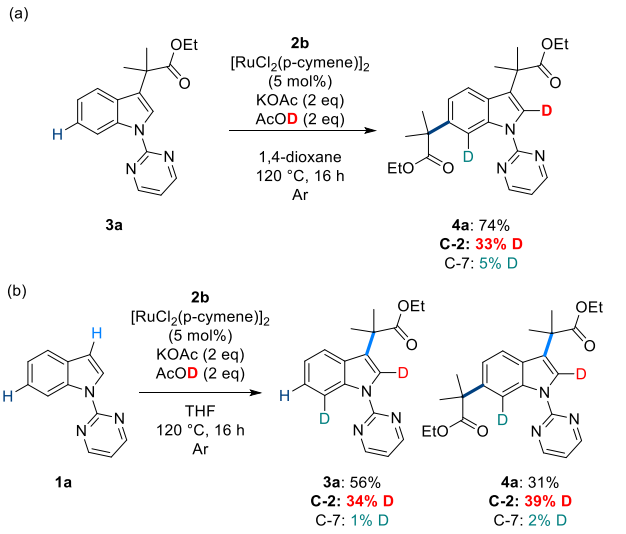
In order to determine reaction mechanism, experimental and computational mechanistic studies were undertaken. Our previous investigations in remote σ-activation methodology proposed a dual cyclometalation and radical pathway.[12c] Here, the presence of a radical mechanism was investigated by the use of a radical trapping agent (Scheme 7). Neither remote C6 functionalization nor one-pot C3/C6 di-functionalization were observed in the presence of stoichiometric TEMPO. One catalytic turnover was also observed using catalytic quantities of TEMPO, suggesting that a redox catalyst is unable to turn over in the presence of the radical trapping agent. As both reactions (Scheme 7a & 7b) were affected by these investigations, it can be postulated that both C3 and C6 alkylation proceed *via* a radical pathway.[21]

Scheme 7. TEMPO studies on remote alkylation of indole derivatives



Deuterium incorporation studies using isotopically labelled AcOD were then performed to determine whether formation of C6 and C3 functionalized products are obtained *via* C2 insertion or C7 insertion (Scheme 8). Deuterium was incorporated into the C2 position in significant quantities (33%, Scheme 8a) and only in negligible amounts at C7 (<5%). This highlights that the C6 functionalization is most likely not accessed through C7 insertion as observed in Shi's work but through a C2 cyclometalation σ-activation pathway.[9] Also seeing that similar D-incorporation is observed in **3a** and **4a** in the one-pot methodology (Scheme 9b), it could be suggested that these are formed through the same linear mechanistic pathway.

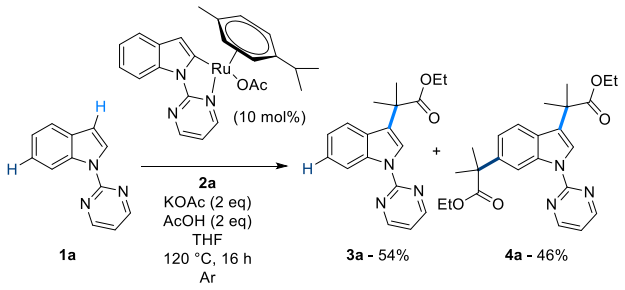
Scheme 8. Deuterium incorporation investigations



The cyclometalated complex of **1a** was synthesized and exposed to the reaction conditions (Scheme 9).[5e] Comparable efficiency to both mono and di-functionalization found previously was observed. This implies that such a cyclometalated species could be part of the catalytic cycle, either as a redox catalyst in radical generation or through a *ortho*-σ-activation catalyst, activating the C3 position for initial radical attack.[22]

In order to elucidate the reasoning behind the exclusive C6 functionalization we employed computational methods. Ritter and co-workers used nucleophilic Fukui indices as a simple method to predict selectivity in aromatic radical reactions in a recent report.[23] We looked to apply this computational approach to the organic structures synthesized in this study as well as the equivalent cyclometalated complexes.

Scheme 9. Remote functionalization using a well-define cyclometalated monomer



In order to do this, the relative Fukui indices were calculated from NBO calculations for carbon atoms in both the organic (non-cyclometalated substrates) and a range of inorganic (cyclometalated at either the C2 or C7 position) structures, shown in Figure 3 (additional structures in the SI).[24] Our relative Fukui indices show the reactivity of carbons towards electrophilic attack with the most reactive carbon site for functionalization highlighted in red.[24]

The inherent reactivity of the organic indole reagent, **1a**, is unsurprisingly held at the C3 position according to the relative Fukui indices. Cyclometalation at C2 (**^{1a}B-C2**) shows that C3 is still the most reactive carbon, however, an increase in relative reactivity of the C6 position is observed. As both these organic and inorganic structures are shown to activate the C3 position, it is still possible for initial C3 radical addition (to form **3a**) to be achieved through an inner sphere or outer sphere mechanism. Cyclometalation at C7 (**^{1a}B-C7**) shows a huge increase in reactivity at the C4 position. As this regioselectivity is not observed experimentally, alongside deuterium incorporation experiment results, it is concluded that this cyclometalated species is not involved in the formation of the C-6 functionalized product (**4a**). A computed free energy difference of 6.3 kcal mol^{-1} between the more stable **^{1a}B-C2** and **^{1a}B-C7**, also confirms the experimental regioselectivity.

Relative Fukui indices were also calculated for the C3 functionalized material (**3a**), again cyclometalated at either the C2 or C7 position. Values for the organic **3a** show that the most reactive site for C-H functionalization is the C4 position. Therefore, a radical addition mechanism to a non-cyclometalated species can be dismissed and consequently this demonstrates that the metal center and cyclometalation are directly responsible for the observed regioselectivity of the reaction. Two conformers of the C2 cyclometalated structure, **^{3a}B-C2** have been optimized and are shown in Figure 4. The most stable conformer, **^{3a}B-C2***, involves coordination of the ester group to the Ru center through the carbonyl oxygen, forcing ring-slippage of the *para*-cymene to η^2 to accommodate this additional binding to **3a**, whilst the acetate coordinates through both oxygen atoms (κ^2). This additional binding of the ester group at the C3 position to the ruthenium stabilizes the organometallic structure by 3.4 kcal mol^{-1}, when compared to **^{3a}B-C2**.

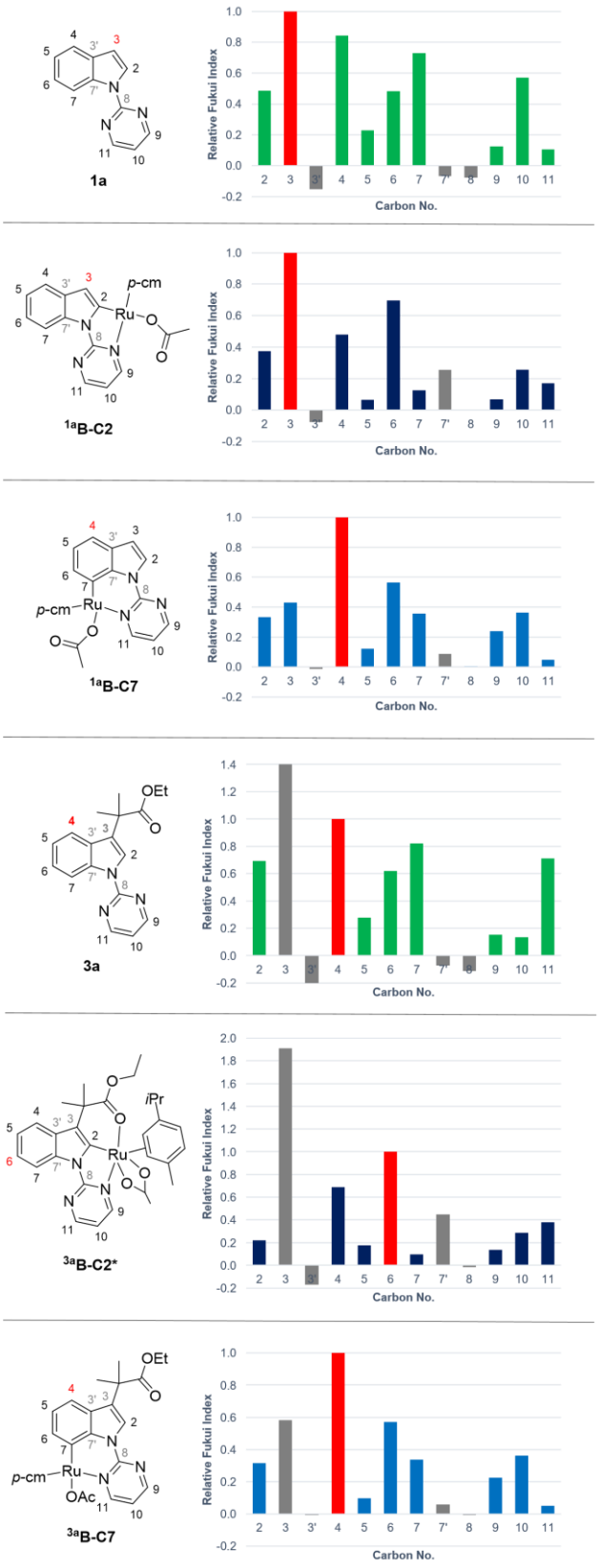


Figure 3. Relative nucleophilicity Fukui indices for organic and inorganic computed structures. Calculations were performed at the BP86/6-31G**&SDD(Ru) level of theory. Fukui indices were calculated with NBO total atomic charges from the optimized neutral structure. Most reactive vacant C-H position is highlighted in red.

The ability of **3a** to access this more stable planar tridentate binding motif through the ester group could explain the improved remote functionalization *via* σ-activation observed for this substrate. Previously, remote functionalization *via* this method has been primarily limited primarily to 2-phenylpyridine due to its strong planar ruthenacycle. Identification of this ancillary stabilization provided by the ester group at C3 presents the opportunity to explore similar structural motifs with this methodology.

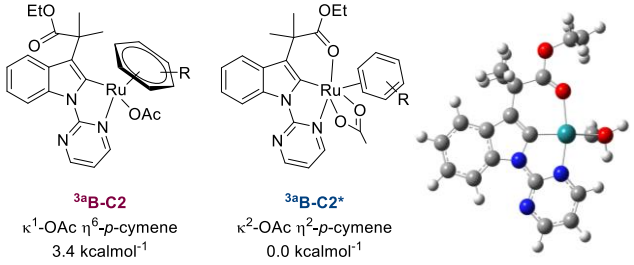


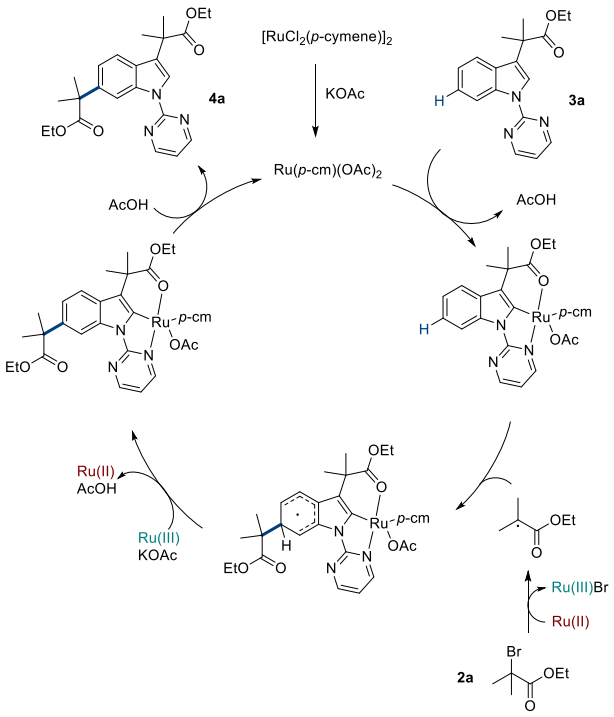
Figure 4. Free energies of optimized conformers ^{3a}**B-C2** and ^{3a}**B-C2*** using BP86/6-31G**&SDD(Ru) in kcal mol^{-1} showing the impact of ester binding. The ball-and-stick structure is of ^{3a}**B-C2*** with the η^2-*para*-cymene omitted for clarity.

Based on results from both computational and experimental investigations, a plausible mechanism is proposed for the remote radical functionalization of **3a** (Scheme 10). The [$RuCl_2$(*p*-cymene)]$_2$ dimer is first broken apart using KOAc to form the proposed catalytically active monomer [Ru(OAc)$_2$(*p*-cymene)] (which is competent in the reaction, see supporting information Scheme S2). Carboxylate assisted cyclometalation at C2 then occurs, including a proposed ring slip of the *para*-cymene to accommodate the primary and ancillary directing groups. A ruthenium(II) catalyst then most likely creates the tertiary alkyl radical *via* single electron transfer.[12c] The alkyl radical then attacks the cyclometalated species at the most activated vacant position, confirmed to be C6 *in silico*. Redox rearomatization then takes place using the ruthenium(III) generated previously and an equivalent of potassium acetate. Protodemetalation then occurs using AcOH to give the C6 C-H alkylated product (**4a**) and reforms the catalytically active monomer.

CONCLUSION

In conclusion we have developed the first remote functionalization of indole derivatives *via* σ-activation. This was achieved using a cyclometalated ruthenium species at the C2 position of the indole. It has been reported that an ester ancillary directing group at C3 was essential for remote C-H alkylation at C6 to occur and yields of up to 92% were achieved applying this methodology. We also reported the one-pot installation of the ester at C3 *via* ruthenium catalysis followed by ruthenium-catalyzed remote C6 functionalization. Initial C3 functionalisation has been shown to proceed *via* a redox ruthenium-catalyzed pathway, as well as remote C6 functionalization *via* radical trapping experiments. Computed Fukui indices were applied to organic and cyclometallated inorganic structures to explain the C6 position as the most reactive C-H site for functionalization. Work is ongoing to apply this template to other remote *meta*-functionalization reactions.

Scheme 10. Plausible mechanism for remote C6 C-H alkylation of 3a



ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and full characterization of compounds is available in the supporting information. Full crystallography data is available *via* the CIF files attached as supporting information.

The Supporting Information is available free of charge on the ACS Publications website.

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NOTES AND REFERENCES

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